Pulmonary Hypertension in Predialysis Chronic Kidney Disease: Frequency and Potential Mechanisms

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Abstract

Background: Pulmonary arterial hypertension (PH) and Chronic Kidney Disease (CKD) both profoundly affect patient outcomes, whether as primary disease states or as comorbid conditions. PH is a common comorbidity in CKD and vice versa. PH is an independent predictor of mortality in such patients. In a recent review, the prevalence of PHT in ESRD patients was reported to be around 40-50% however, the epidemiological data for this disorder in earlier stages of Chronic Kidney Disease (CKD) and the risk factors associated with its presence are scarce.

Aim: To evaluate the frequency of pulmonary hypertension among chronic kidney disease nondialysis dependent patients and to compare clinical and metabolic variables among those patients with the control group to search for possible mechanisms.

Subjects and Methods: 40 CKD patients (55% men, 45% women; mean age, 42.9 ± 15.13 years) with. According to the magnitude of Glomerular Filtration Rate (GFR) decrease, the CKD patients have divided into 3 groups: (1) 2 patients with a GFR of 89-60ml/min; (2) 6 with a GFR of 59-45ml/min; (3) 32 with a GFR of 44-15ml/min. A control group consisted of 40 individuals with preserved kidney function (a GFR of >90 ml/min). Physical examination and echocardiography were performed in all the patients. The serum concentrations of homocysteine and serum PTH were determined.

Results: PH was detected in 20 (50%) of the 40 patients with CKD. As CKD progressed, the frequency of pulmonary hypertension in Groups 1, 2, and 3 increased, amounting to 18.2%, 24.2%, and 35%, respectively.

Conclusion: This study demonstrated a high frequency of pulmonary hypertension among patients with CKD without dialysis.

PULMONARY Hypertension (PH), a cardiovascular disorder characterized by elevated Pulmonary Artery Pressure (PAP), was found to be an unrecognized threat in a considerable proportion of patients with End-Stage Renal Disease (ESRD) [1].

In recent years, Pulmonary Hypertension (PH) in Chronic Kidney Disease (CKD) patients is gaining interest because of its apparent high prevalence and its significant role in the outcome, principally in patients undergoing Hemodialysis (HD) [2]. This condition usually remains asymptomatic and sometimes is misdiagnosed over a period of time until right ventricular dysfunction begins to manifest by worsening fatigue, dyspnea and syncope [3].

PH might be induced and/or aggravated by left ventricular disorders and risk factors typical of CKD, including volume overload, arteriovenous fistula, sleep-disordered breathing, exposure to dialysis membranes, endothelial dysfunction, vascular calcification and stiffening, and severe anemia [4], oxidative stress and alteration of vasoactive mediators such as nitric oxide and endothelin-1 [5].

Therefore, this study was conducted to show the frequency of pulmonary hypertension in various CKD non dialysis dependent stages with the po-
tential mechanisms that can lead to pulmonary hypertension in this population group.

Additionally a correlation between secondary hyperparathyroidism and PH have been reported, PH induced by increased parathyroid hormone associated with vascular calcification have been reported in CKD [6].

It is believed that hyperhomocysteinemia may cause changes in vascular endothelium, mainly mediated by the toxic effect of oxidized forms of this amino acid [7].

The evaluation of plasma homocysteine levels has been reported as a biomarker for endothelial dysfunction, linking its increase to severe diseases with endothelial injuries, such as Pulmonary Hypertension (PH) [8]. This is characterized by pulmonary arterial hypertension, and may reflect in dysfunction and right ventricular heart failure [9].

Patients and Methods

This study was conducted in Faculty of Medicine, Assuit University Hospital from Feb. 2016 – August 2016.

It is an observational case-control study occurred in outpatient nephrology and internal medicine clinics included 80 candidates, 40 patients with different stages of pre-dialysis chronic kidney disease and 40 healthy volunteers based on exclusion and inclusion criteria where all patients with chronic kidney diseases non dialysis dependent and above or equal to 18 years were included but smokers, cardiovascular (coronary artery diseases and valvular heart diseases) pulmonary diseases (chronic obstructive lung diseases, chest wall or parenchymal lung diseases).

Which leads to pulmonary hypertension, also connective tissue diseases and patients with liver diseases were excluded.

Once all the criteria were satisfied, a written informed consent was taken and the patient was included in the study. A detailed history and physical examination of every patient including age, sex, duration of illness, etiology of chronic kidney disease, type of treatment received, associated comorbidity as diabetes and hypertension. Each patient underwent routine investigations like complete haemogram, serum electrolytes (Ca, PO4), renal function tests (BUN, serum creatinine), parathyroid hormone and homocysteine assays.

The laboratory assays were done by the following methods:

- Complete blood picture: By Cell Dyn 3700 Automated blood cell counter.
- Serum urea, creatinine, calcium and phosphorus: Cobas Integra 400-Plus clinical chemistry analyzer.
- Plasma parathyroid hormone level: By Sandwich chemiluminescence immunoassay using Maglumi 2000 Plus autoanalyzer (the kit supplied by Shenzhen New Industries, China, Catalog number 130211001M).
- Plasma homocysteine level: By ELISA technique using SinoGeneClon Kit, China (Catalog number SG-10387).

Test principle: Purified Human Homocysteine (HCY) coat the microtiter plate making solid phase antibody. HCY in the samples added to the wells combine HCY antibody with labeled HRP to form antibody-antigen-enzyme complex. After washing, TMB substrate was added, which become blue at HRP enzyme catalyzed reaction. The reaction was terminated by the addition of a stop solution and the color change was measured at a wave length of 450nm. The concenyration of HCY in the samples is then determined by comparing the optical density of the samples to the standard curve.

Transthoracic Doppler echocardiography:

Every patient had Undergone a complete two-dimensional and Doppler echocardiography study, Echo-Doppler studies can provide an estimate of the PASP, a surrogate of mean pulmonary artery pressure, which is calculated on the basis of the tricuspid regurgitation jet velocity. In the absence of pulmonary stenosis, Right Ventricular Systolic Pressure (RVSP) approximates PASP by echo-Doppler. PASP (assumed to be equal to RVSP) can be then estimated by calculating RVSP with the Bernoulli equation formula 4TRV (tricuspid regurgitant velocity) + RAP (right atrial pressure). Other echocardiographic measurements, including the right ventricular wall thickness and left atrial dimension and LV systolic and diastolic function, valvular apparatuses assessment and detection of any pericardial effusion all give additional, precious information for the diagnosis of PH by echo-Doppler.

Statistical analysis:

The collected data will be analyzed statistically using IBM-SPSS Version 20. Continuous data will be expressed in form mean ± SD and analyzed by using student t-test while nominal data will be
expressed in form of frequency and proportion and compared by Chi-square test correlation of PASP with echocardiography findings and homocysteine level will be tested by using Pearson’s correlation.

**Results**

Our results showed a highly statistically significant decrease in hemoglobin, and statistically significant increase in blood urea nitrogen, creatinine, phosphorous, C-reactive protein, parathyroid hormone, homocysteine between the studied chronic kidney diseases group and the control group, but no statistically differences were found between both groups with respect to age, BMI and serum calcium. A high prevalence of pulmonary hypertension (SPAP >25mmHg) was demonstrated among 20 patients in the chronic kidney diseases patients, which represent 50% in CKD group which had a highly statistically significant increase than in the control group where 4 patients only had pulmonary hypertension in the control group. An interesting result in our study showed also is that the more decrease in the glomerular filtration rate the more grade of pulmonary hypertension where the patients with grade III chronic kidney disease had moderate hypertension which represents 2.5% of the CKD patients. Our results also showed there is a negatively strong statistically significant correlation between PASP and hemoglobin level and ejection fraction where the decrease in the hemoglobin level and the decrease in the ejection fraction is strongly associated with the development of any grade of PASP.

Also, our results showed that there is a positively strong statistically significant correlation between PASP and LVDD, LVSD and LAD. In addition to the previous results, our study revealed a positive significant correlation between PASP and parathyroid hormone and PASP and homocysteine.

**Table (1): Baseline demographic and clinical parameters of the studied groups.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Study group (n=40)</th>
<th>Control group (n=40)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>42.09±15.13</td>
<td>35.13±8.45</td>
<td>0.00</td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>22 (55%)</td>
<td>21 (52.5%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Female</td>
<td>18 (45%)</td>
<td>19 (47.5%)</td>
<td></td>
</tr>
<tr>
<td>BMI:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Under weight</td>
<td>25.09±5.32</td>
<td>24.69±2.96</td>
<td>0.33</td>
</tr>
<tr>
<td>Normal</td>
<td>21 (52.5%)</td>
<td>19 (47.5%)</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>17 (42.5%)</td>
<td>19 (47.5%)</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin level (g %)</td>
<td>9.13±2.27</td>
<td>13.37±1.70</td>
<td>0.00</td>
</tr>
<tr>
<td>Platelets count (X103)</td>
<td>284.60±108.7</td>
<td>277.30±50.19</td>
<td>0.71</td>
</tr>
<tr>
<td>Urea (µmol/l)</td>
<td>24.32±13.39</td>
<td>5.05±2.05</td>
<td>0.00</td>
</tr>
<tr>
<td>Creatineine (µmol/l)</td>
<td>351.17±110.04</td>
<td>83.87±31.43</td>
<td>0.00</td>
</tr>
<tr>
<td>Calcium (mg%)</td>
<td>8.98±5.96</td>
<td>10.22±0.76</td>
<td>0.19</td>
</tr>
<tr>
<td>Phosphorous (mg%)</td>
<td>5.14±2.01</td>
<td>1.97±0.84</td>
<td>0.00</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>7.28±2.09</td>
<td>±1.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Parathyroid level (pg/ml)</td>
<td>84.12±12.93</td>
<td>15.04±9.08</td>
<td>0.02</td>
</tr>
<tr>
<td>Homocysteine (ml/l)</td>
<td>13.38±3.04</td>
<td>7.85±2.89</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Table (2): Frequency of different grades of pulmonary hypertension in the studied population.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Study group (n=40)</th>
<th>Control group (n=40)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASP (mmHg)</td>
<td>30.35±8.66</td>
<td>13.40±5.30</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Grade of PH:

<table>
<thead>
<tr>
<th>Grade (mmHg)</th>
<th>Study group (n=40)</th>
<th>Control group (n=40)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (&lt;25mmHg)</td>
<td>20 (50%)</td>
<td>36 (90%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Mild (25-50mmHg)</td>
<td>19 (47.5%)</td>
<td>4 (10%)</td>
<td></td>
</tr>
<tr>
<td>Moderate (50-70mmHg)</td>
<td>1 (2.5%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Severe (&gt;70mmHg)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

Table (3): Correlation of PASP with hemoglobin, LVDD, LVSD, EF and LA.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Strength of association</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>−0.60</td>
<td>0.00</td>
</tr>
<tr>
<td>LVDD</td>
<td>0.23</td>
<td>0.03</td>
</tr>
<tr>
<td>LVSD</td>
<td>0.21</td>
<td>0.01</td>
</tr>
<tr>
<td>LAD</td>
<td>0.63</td>
<td>0.00</td>
</tr>
<tr>
<td>EF</td>
<td>−0.52</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Discussion

The decrease in kidney function may be a trigger for the development of PASP disturbance. The Doppler-estimated PASP increased inversely to renal function. In kidney disease, a series of complications appears eventually, such as anemia, endothelial dysfunction, LV dysfunction, and volume overload. Severe anemia, an established cardiovascular risk factor in CKD, may extend its impact to pulmonary circulation [5]. In practice any condition which leads to shunt of the blood from the left side of the heart to the right side will lead eventually to increase in the cardiac output and though will lead to increase in the pulmonary blood flow and thus it will result in pulmonary hypertension [10]. Previous studies showed that pulmonary hypertension is a very common complication in chronic kidney diseases patients especially those who had reached end stage renal disease [11].

In the present study which is considered a new study which tries to detect the frequency, and the possible etiologies of pulmonary hypertension in predialysis patients as this topic is underestimated in many studies which give greater concern to those on haemodialysis.

The early detection of pulmonary hypertension and recognition of its causes may help to delay its occurrence and progression by good treatment as many causes may be preventable and treatable.

On the other hand, severe pulmonary hypertension may hinder or even leads to transplantation failure.

We found in our study that pulmonary hypertension occurred early in the disease even before the symptoms of CKD had been prominent but the severity of former correlates negatively with the eGFR.

There were multiple etiologies of PH in the present study which will be discussed separately.

Decreased eGFR and hemoglobin level may increase pulmonary artery pressure due to volume overload and increased pulmonary blood flow due to anemia [12].

Also this result was nearly in agreement with those reported by Genctoy et al., [13].

We observed that grade IV CKD had the highest frequency among our patients and grade I had the lowest frequency and this owing to that CKD is considered a silent disease in its early grades and has a non specific symptoms; added to low awareness of our patients and low socioeconomic status.

In present study, we found that; the patients group had a higher mean Pulmonary Artery Systolic Pressure (PASP)-compared to the control group (30.35±8.66mmHg versus 13.40±5.30) with a statistically significant difference (p-value=0.00) and the prevalence of PH was 50% (20/40), in our patients. eGFR was calculated using the modification of diet in renal disease study equation.

The prevalence of PH was higher in patients with stage 3-4 CKD compared with stage 1-2 CKD.

As grade IV CKD had the highest frequency of PH as 15 (46.87%) had a mild pulmonary hypertension and one patient (3.1%) had a moderate degree of PH, on the other hand, grade II CKD had the lowest frequency i.e one patient had mild degree of PH.

This result was nearly in agreement with those reported by Yang and Bao., [5] PH prevalence reached 48.15% (13/27) in the GFR <60mL/min/1.73m² group, the GFR ≥60mL/min/1.73m² group (with less renal injury) still has a prevalence of 23.76%, 24 of 101 CKD patients.

Also, our results were nearly in agreement with those reported by Havlucu et al., [6] PSAP >35 mmHg was founded in 39.1% (9/23) of predialysis patients (29.5±9.5 mm Hg).

The causes of pulmonary hypertension in the studied population was multifactorial, hyperparathyroidism, hyperhomocystenamia, endothelial
dysfunction and inflammatory process as well as left ventricular dysfunction were recorded.

In our study that there was statistically significant correlation between PSAP and level of parathyroid hormone.

This was inaccordance with Ulrich et al., [14] who found a particularly striking elevation of the mean PTH serum levels in patients with PH.

Also, these results were nearly in agreement with those reported by Demir et al., [15] who was reported that hyperparathyroidism due to low vitamin D levels was associated with increased pulmonary artery pressure.

But these results were not in agreement with those reported by Amin et al., [16] whose investigations of the parathyroid gland activity revealed no difference between patients with and without PH, with regards to values of PTH, but this study was done in patients with Chronic Renal Failure (CRF) receiving regular haemodialysis.

In our study, that there was statistically significant positive correlation between PSAP and level of homocysteine.

In our study, that there was statistically significant positive correlation between PSAP and level of homocysteine.

This result was nearly in agreement with those reported by Arroliga et al., [8]. There was a correlation between the Homocysteine levels and PH.

Volume overload, implicated in LV disorders and in the high venous return, and LV diastolic dysfunction, an alteration found in patients with CKD to increase pulmonary venous and arterial pressure [17], may together induce PH by increasing pulmonary blood flow and adversely affecting LV function.

In the present study, correlation between PASP and both LVDD and LVSD While EF had a negative significant correlation with PASP.

These results are in concordance with Yigla et al., [18]. Havlucu et al., [6] and Abdallah et al., [19], and similar results reported by Beigi et al., [20], Fabbian et al., [21] and Emara et al., [22] reported an inverse correlation between PAP and ejection fraction.

High C-Reactive Protein (CRP) is independent risk of mortality in patients with Chronic Kidney Disease (CKD).

C-Reactive Protein (CRP) levels are elevated in patients with kidney disease [23] and are an independent predictors of cardiovascular mortality in this patient population [24]. CRP in particular, are independent predictors of the future risk of outcomes both in the general population and among patients with kidney disease.

In our study, although there was positive correlation between PASP and CRP but of no significant value as $p$-value was >0.05, and this may be due to small sample size of our patients.

This result was nearly in agreement with those reported by Pereira et al., [25].

Lastly, the results of this study suggest that a significant proportion of pre-dialysis CKD patients showed functional abnormality in their pulmonary circulation. Apart from hyperhomocysteinemia, lower EF%, secondary hyperparathyroidism, anemia, hyperphosphatemia, and CRP and inflammation may contribute to increasing PAP in patients with CKD.

Study limitations:

This study has certain limitations. The exclusion criteria used in our protocol resulted in a small study group, since the majority of patients with CKD had concomitant cardiac or pulmonary disease. The exclusion of patients with CKD with cardiac or pulmonary disease from the analysis was a methodological necessity. Moreover, PASP was measured by a non-invasive method, Doppler echocardiography, with-out obtaining direct invasive measurements (e.g. right heart catheterization). However, measurements of PASP by the applied Doppler echocardiographic method have been reported to have a good correlation with measurements obtained by invasive methods in some studies.

References


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ارتفاع ضغط الشريان الرئوي في مرضى الارتلاع الكلوي المزمن

هو إرتفاع ضغط الدم الرئوي (PH) هو إرتفاع ضغط الشريان الرئوي يمكن أن يكون نتيجة لضعف قلب، الرئة، أو إضطربات جهازية.

في هذا المقال، وجدنا أن نسبة الوفاة في مرضى إرتفاع ضغط الدم الرئوي في مرضى الكلوي أعلى من نظراهم ب دون إرتفاع ضغط الدم الرئوي، والسبب الرئيسي يعتمد على سببته. ولهذا السبب، قد حددنا السبب الرئيسي في كلارا، وهو في مرضى الذين يعانون من القصور الكلوي المزمن.

حمض الأمين هو من الحمض الأميني الكريبتين. تتضمن بعض الحمض الأميني الميثونين. يتمثل الدماغي وترشيح الكلى يلعب دورًا في إزالة الحمض الأميني من الدم.

إحراز مستوى الحمض الأميني في الدم يمكن أن يؤدي إلى احتراء عضلة القلب الحاد، تخثر الدم، وتصيب الشرايين.

ويعتقد أن فرط الهرمونات في الدم قد يسبب تغييرات في بطانة الأوعية الدموية، وربما زيادة الكريبتين في الدم بما في ذلك وظيفة بطانة الأوعية الدموية، وربما زيادة لكلاً من هذه الارتفاع ضغط الدم الرئوي.

الهدف من الدراسة: تقييم مدى إرتفاع ضغط الدم الرئوي Первый بolesti élémen برضي من الأسباب المرضية المحتملة.

لمقارنة المتغيرات والمثبطات الفي القيصرية بين المرضى مع ودون إرتفاع ضغط الدم الرئوي للبحث عن الأسباب المرضية المحتملة.

نتيجة البحث: في هذه الدراسة، تم تحديد الأسباب المرضية المحتملة التي تؤدي إلى إرتفاع ضغط الدم الرئوي في مرضى الارتلاع الكلوي المزمن في حالة قبل الفعيل الكلوي المزمن.

وقد شملت هذه الدراسة على 100 مريض يمكن أن يكون من قصور كلوي مرحالة المختلفة، و 100 أصحاء لمقارنة المتغيرات والمثبطات الفي القيصرية بين المرضى مع و دون إرتفاع ضغط الدم الرئوي.

وقد وجدت الدراسة أن نسبة إرتفاع ضغط الدم الرئوي سجلت (40%) من المرضى الخاضعين للدراسة لديهم في حالة قبل الفعيل الكلوي المزمن.

أشارت هذه الدراسة إلى الأسباب المرضية لإرتفاع ضغط الدم الرئوي في مرضى الارتلاع الكلوي المزمن منها، إختلال الهرمونات، الأوعية الدموية المزمنة، و فقر الدم، زيادة نسبة الفسفور في الدم، اختلال الالتباس الأيسر، و فرط الهرمونات في الدم، إرتفاع فرص الفشل الكلوي المزمن، وزيادة البروتين والانهيار على التوالي.